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Review article

The impact of gut hormones on the neural circuit of appetite and satiety: A systematic review

Davide Zanchi[a], Antoinette Depoorter[b], Laura Egloff[a], Sven Haller[c,d,e,f], Laura Mählmann[a], Undine E. Lang[a], Jürgen Drewe[g], Christoph Beglinger[g], André Schmidt[a,*], Stefan Borgwardt[a,*]

[a] University of Basel, Department of Psychiatry (UPK), CH-4012 Basel, Switzerland
[b] Division of Neuropaediatrics & Developmental Medicine, University Children's Hospital, Basel, Switzerland
[c] Centre de Diagnostic Radiologique de Carouge CDRC, Geneva, Switzerland
[d] Faculty of Medicine of the University of Geneva, Switzerland
[e] Department of Surgical Sciences, Radiology, Uppsala University, Uppsala, Sweden
[f] Department of Neuroradiology, University Hospital Freiburg, Germany
[g] Department of Research, St. Claraspital, Switzerland

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ABSTRACT

The brain–gut-axis is an interdependent system affecting neural functions and controlling our eating behaviour. In recent decades, neuroimaging techniques have facilitated its investigation. We systematically looked into functional and neurochemical brain imaging studies investigating how key molecules such as ghrelin, glucagon-like peptide-1 (GLP-1), peptide tyrosine–tyrosine (PYY), cholecystokinin (CCK), leptin, glucose and insulin influence the function of brain regions regulating appetite and satiety.

Of the 349 studies published before July 2016 identified in the database search, 40 were included (27 on healthy and 13 on obese subjects).

Our systematic review suggests that the plasma level of ghrelin, the gut hormone promoting appetite, is positively correlated with activation in the pre-frontal cortex (PFC), amygdala and insula and negatively correlated with activation in subcortical areas such as the hypothalamus. In contrast, the plasma levels of glucose, insulin, leptin, PYY, GLP-1 affect the same brain regions conversely. Our study integrates previous investigations of the gut-brain matrix during food-intake and homeostatic regulation and may be of use for future meta-analyses of brain-gut interactions.

1. Introduction

The brain–gut axis is an interdependent system that affects neural function and controls our eating behaviour through biochemical signalling between the endocrine and nervous system through hormonal peptides in the gastrointestinal tract (Huda et al., 2006; Steinert et al., 2017; Wren and Bloom, 2007). The two main families of gastrointestinal (GI) hormones are a) Appetite stimulators, such as ghrelin, a 28 amino acid peptide that promotes meal initiation by increasing appetite and hunger feelings (Cummings et al., 2001; Kojima et al., 1999), and b) Satiety stimulators, such as the gut hormones glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY3-36) cleaved from PYY1-36, cholecystokinin (CCK) and leptin that signal the brain to decrease hunger and promote meal cessation (Figlewicz, 2003; Woods et al., 1998). Next to these GI hormones, insulin, a pancreatic hormone, as well as insulin regulated glucose, play a major role in human metabolism and eating behaviour (Figlewicz, 2003; Woods et al., 1998).

Neuroimaging techniques have greatly facilitated the investigation of human brain–gut interactions in recent decades. Pioneering studies (Liu et al., 2000) combining functional magnetic resonance imaging (fMRI) with hormonal blood analyses have demonstrated a direct link between changes in plasma concentrations in hormones and modifications in brain regions that are part of the neural circuit of appetite, as identified by Woods et al. (1998). In particular, increased insulin plasma levels are linked to changes in brain activity in the anterior cingulate cortex (ACC), in the orbitofrontal cortex (OFC), in the sensorimotor cortex and in the hypothalamus. On the other hand, it is well established that ghrelin (Malik et al., 2008) acts through the

Abbreviations: ACC, Anterior Cingulate Cortex; ASL, Arterial Spin Labelling; BOLD, Blood Oxygen Level Dependent; CBF, Cerebral Blood Flow; CNS, Central Nervous System; CSF, Cerebrospinal Fluid; dACC, Dorsal Anterior Cingulate Cortex; fMRI, Functional Magnetic Resonance Imaging; OFC, Orbitofrontal Cortex; OGTT, Oral Glucose Tolerance Test; PET, Positron Emission Tomography; PFC, Pre-frontal cortex; rsfMRI, Resting State fMRI; vmPFC, Ventromedial Prefrontal Cortex; vmPFC, Ventromedial Prefrontal Cortex

* Corresponding authors.
E-mail addresses: andre.schmidt@unibas.ch (A. Schmidt), stefan.borgwardt@upkbs.ch (S. Borgwardt).

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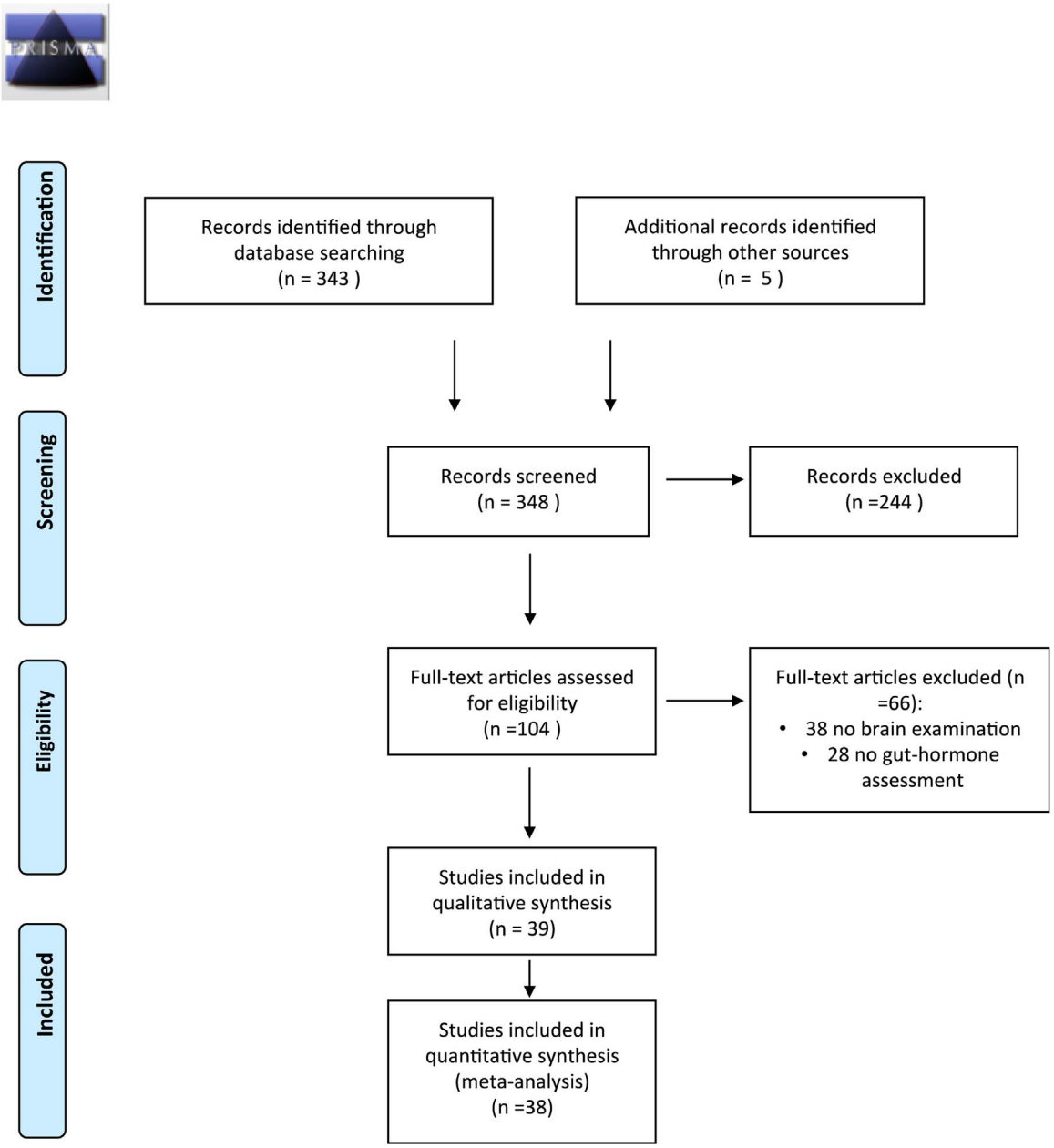

Fig. 1. Flowchart of the selection procedure.

hypothalamus to influence several brain regions involved in the food-reward pathway, including the ventral tegmental area (VTA), nucleus accumbens, amygdala, and hippocampus (Abizaid et al., 2006; Diano et al., 2006; Nakazato et al., 2001). These findings suggest that different gut peptides divergently modulate brain activation in the neural circuit controlling appetite and thereby regulate our prospective eating behaviour.

However, studies often report inconsistent findings making a general interpretation difficult. There are different reasons for the discrepancies: study designs have been variable with different nutrients ingested (stimulating different gut peptides) and different paradigms have been used during fMRI examination.

A general overview of the different studies and of the methodologies used in the field is therefore necessary.

In the present study, we systematically reviewed functional and neurochemical brain imaging studies investigating how the main gut peptides (ghrelin, PYY3-36, leptin, GLP-1 and CCK), insulin and glucose influence activation in brain regions regulating appetite and satiety in healthy and obese subjects. On the basis of the findings of these studies, we hypothesised that the brain areas involved in the food-reward circuit, such as the anterior cingulate cortex (ACC), the insula and the hypothalamus, are activated in opposite directions, by gut peptides linked to satiety or to appetite stimulation.

2. Methods

To ensure high quality reporting, PRISMA guidelines for systematic reviews were followed (Moher et al., 2015).

2.1. Search strategy

An electronic search was performed using the PubMed database. The following search terms were used: ((ghrelin OR glucose OR insulin OR peptide YY OR leptin OR GLP-1 OR cholecystokinin) AND (appetite OR satiety)) AND (mri OR fmri OR pet OR spect OR imaging OR neuroimaging). All studies published before July 2016 were included,